EXHIBIT 42

Report of Jonathan Borak, MD, DABT
June 02, 2017

I. Introduction

1. I am a Clinical Professor of Epidemiology & Public Health and Clinical Professor of Medicine at Yale University, a faculty member of the Yale Occupational and Environmental Medicine Program, and Adjunct Associate Professor of Medicine at The Johns Hopkins University. I am also President of Jonathan Borak & Company, a consulting firm in New Haven, Connecticut. My CV is attached at Exhibit A and a list of my previous deposition and trial testimony is attached at Exhibit B.

2. I received my B.A. with honors from Amherst College in 1968 and my M.D. from New York University in 1972. I am Board Certified in Internal Medicine, Preventive Medicine (Occupational Medicine) and Toxicology (American Board of Toxicology). I am a Fellow of the American College of Physicians, the American College of Occupational and Environmental Medicine, the Royal College of Physicians of Canada, the Academy of Toxicological Sciences, and the American Industrial Hygiene Association.

3. Among my Yale activities, I have directed and taught two required graduate-level courses (Principles of Toxicology and Principles of Risk Assessment) for nearly twenty years. I also lecture in a number of other graduate-level courses including occupational epidemiology, environmental exposure assessment, and environmental health. Included in this teaching are the interpretation of epidemiological data and inference of causation. From 2002-2010 I was Director of the Yale University Interdisciplinary Risk Assessment Forum. I also participate in the supervision and training of Fellows and other resident physicians in the Yale Occupational and Environmental Medicine Program.

4. I served as an elected Director of the American College of Occupational and Environmental Medicine (ACOEM) from 1999-2002 and as Chair of the ACOEM Council on Scientific Affairs from 1999-2012. I was a founding member of US EPA's National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances, a member of the National Research Council Committee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents, a member of a National Institute of Environmental Health Sciences review panel on Partnerships for Environmental Public Health, and a member of an External Review Panel for the National Institute for Occupational Safety and Health. I was President of the Occupational and Environmental Medicine Association of Connecticut, President of the Connecticut College of Emergency Physicians, and Chairman of the Connecticut State Medical Society Committees on Preventive Medicine and on Emergency Medical Services.

5. I am a member of the Editorial Boards of Journal of Occupational and Environmental Medicine, Journal of Occupational and Environmental Hygiene, and

Occupational Medicine. I served as Associate Editor of OEM Report, as a member of the Editorial Board of the American Industrial Hygiene Association Journal, and currently serve as a peer reviewer for numerous medical and scientific publications.

6. I have written numerous books, monographs, book chapters, peer-reviewed articles and other publications on a range of topics in occupational medicine, toxicology, epidemiology, industrial hygiene and public health.

7. I have received numerous awards from ACOEM including: the President's Award in 1994, 2000 and 2008; the Adolph G. Kammer Merit in Authorship Award in 2003; the Robert A. Kehoe Award of Merit in 2004; and the George H. Gerchman Memorial Prize in 2005. I also received the Harriet Hardy Award from the New England College of Occupational and Environmental Medicine in 2012.

8. In the present matter, I was asked by Mr. Corey Gordon of Blackwell Burke to review expert reports, depositions and other materials concerning the use of forced air warming devices (FAW) (such as the Bair Hugger) during surgery and any associated risks of surgical site infections (SSI). I was also asked to review the expert report of Dr. Jonathan Samet and Dr. William Jarvis and, in light of these reports, to opine as to whether there is sufficient evidence to support the general proposition that use of the Bair Hugger (BH) during orthopedic surgery causes or contributes to increased rates of post-operative SSI in patients who undergo total hip and total knee arthroplasty procedures. My company, Jonathan Borak & Company, is compensated at a rate of $550 per hour for my time in reviewing materials and preparing this report and $600 per hour for testimony.

I offer my opinions herein to a reasonable degree of medical and scientific certainty.

9. Accordingly, I reviewed the expert reports and testimony listed below:

Expert Reports

Dr. Jonathan M. Samet	March 30, 2017
Dr. William R. Jarvis	signed but undated
Dr. Theodore Holford	June 1, 2017
Dr. Richard Wenzel	June 2, 2017

Deposition Transcripts and Exhibits

Mr. Mark Albrecht (Vol 1)	October 7, 2016
Mr. Mark Albrecht (Vol 2)	November 12, 2016
Dr. Scott Augustine	March 31, 2017
Dr. Andrew John Legg	December 1, 2016
Dr. Paul McGovern (Vol 1)	January 4, 2017
Dr. Paul McGovern (Vol 2)	January 5, 2017
Dr. Christopher Nachtshteim	November 29, 2016

10. I also reviewed a large number of scientific reports related to surgical warming devices, operating room procedures, surgical complications and infections, and other related medical and scientific issues. Specific publications on which I rely are cited in my report.

II. The Samet Report

11. In his report, Dr. Samet embraced the "sufficient-component-cause model" as the methodological basis for his general causation opinion that use of BH during surgery increases the probability of deep joint infection. In particular, he proposed that use of BH increased the probability "compared to what that probability would have been, absent the utilization of the BH device during hip and knee arthroplasties". He went on to state that there were actually two different comparisons to consider: a) use of BH versus no specific warming device; and b) use of BH compared to a non-FAW device.

11a. There is sufficient evidence that warming surgical patients to prevent hypothermia and maintain normothermia reduces rates of SSI, and thus the use of intraoperative warming has become a standard of current surgical care. For example, the following is a conclusion from the CDC's *Guideline for the Prevention of Surgical Site Infection, 2017* (1):

> "Maintain perioperative normothermia. (Category IA – strong recommendation; high to moderate-quality evidence)"
>
> "High-quality evidence suggested a benefit of patient warming over no warming."

Likewise, the World Health Organization recommends the use of warming devices in the operating room (2):

> "The panel suggests the use of warming devices in the operating room and during the surgical procedure for patient body warming with the purpose of reducing SSI (conditional recommendation, moderate quality of evidence)."

In addition, published findings from two random control trials document that use of BH to maintain intraoperative normothermia reduced the risk of SSI (3;4). Moreover, I am not aware of any basis to propose that use of BH poses increased risks of surgical infection compared to "no specific warming device".

Therefore, the hypothetical comparison of BH vs. no warming device is not relevant to the current dispute.

11b. The alternative comparison, whether use of BH results in increased rates of SSI compared to use of a non-FAW device, all other things being equal, is the central question here. That question is amenable to empirical assessment,

> including whether there is sufficient evidence of a significant difference between the two methods, and if so whether there is sufficient evidence to generalize that conclusion.[1]

But, as discussed below, there is insufficient evidence to demonstrate that FAW increases the probability of deep joint infection under either scenario. That was the conclusion of the recent CDC *Guideline for the Prevention of Surgical Site Infection, 2017* (1). Likewise, the nonprofit ECRI Institute recently concluded:

> "Based on our focused systematic review of the published literature, we believe that there is insufficient evidence to establish that the use of FAW systems leads to an increase in SSIs compared to other warming methods." (5)

And in addition, the following statement is from a Continuing Education statement by the Association of periOperative Registered Nurses (AORN):

> "Our review uncovered no conclusive evidence that the use of forced-air warmers increases the risk of SSIs". (6)

12. Dr. Samet illustrated the use of that model in his Figure 2 ("Adaptation of Sufficient Component Cause Mode to Deep Joint Infection Risk"), which he described as a "hypothetical [that] shows how the presence of BH device increases risk". Two aspects of this illustration should be noted:

> **12a**. As proposed, his model addresses "how the presence of BH device increases risk"; but the relevant question is not how, but whether it increases risk and if so, to what extent. In other words, the model that he describes prejudges the central question: does use of BH result in increased rates of surgical infections?
>
> **12b**. In Figure 2b, Dr. Samet presented and contrasted three alternative "Sufficient Component Causes" for development of post-operative deep joint infections. The first two Causes differ by the inclusion of "surgical procedure factors" in the second, but not the first. The second and third Causes differ in two ways: BH is a component of the third Cause but not the second; and "surgical procedure factors" is a component of the second Cause but not the third. That third Cause, which ignores "surgical procedure factors", is the one that Dr. Samet proposed as showing "how the use of the BH device increases risk for disease" and on which his general causation opinion depends:

[1] Even if there were sufficient evidence to conclude a difference between two alternative warming methods, it would not necessarily indicate that the inferior method "caused" the adverse outcomes (i.e., SSI). Instead, it might be a question of the relative efficacies of two beneficial methods. For example, both BH and non-FAW might be beneficial, as suggested by the evidence that maintenance of body temperature during surgery reduces risks of SSI, but one might be more beneficial than the other. It is not obvious that in such a case "less efficacy" should be seen as equivalent to causation of the adverse effect. In that case, both methods could be seen as positively contributing to the public health, although one might be preferred.

> "With regard to the question of general causation, evidence is considered as to whether evidence supports the existence of Cause 3 in Figure 2."

It might be suggested that his ignoring of "surgical procedure factors" in Cause 3 of Figure 2 simply reflected limitations in Dr. Samet's effort to illustrate his method. However, as discussed below, it is essentially the analytical approach that he actually adopted in his analysis of the McGovern study, which he characterized as "the one directly relevant observational study in the peer-reviewed literature". His opinion on that critical report relied on only a univariate analysis of BH vs. a non-FAW device, while ignoring a variety of other relevant "surgical procedure factors".

13. Dr. Samet also described his "framework for causal inference", four elements of what are often referred to as the "Hill Criteria" (7): temporality; strength of association; consistency; and coherence. He proposed, and I agree, that concern about temporality is not an issue here because, by definition, use of warming devices during surgery precedes the development of post-operative SSI. Thus, his "framework" specifically includes the other three elements, which I will reference in my discussion below.

III. Validity

14. To be meaningful, an inference of causality necessarily assumes that the evidence and data supporting that inference are valid. Likewise, if the underlying facts are not valid, then it follows that inferences which rely on those facts would also not be valid. Accordingly, concerns about the validity of studies on which an inference is based are also concerns about the validity of that inference.

15. The validity of a study is usually described as comprised of two components, *internal validity* and *external validity*. The following description of those two components is from the third edition of a classic epidemiology textbook by Rothman et al (8):

> "The validity of a study is usually separated into two components: the validity of the inferences drawn as they pertain to the member of the source population (*internal validity*) and the validity of the inferences as they pertain to people outside that population (*external validity*)." (p.129)

A similar description is found in the most recent edition of *Reference Manual on Scientific Evidence* (9).

> "*Internal validity* is about the specifics of a particular study… *External validity* is about using a particular study or set of studies to reach more general conclusions. (p.222)

Likewise, the following description is taken from the 2016 edition of *A Dictionary of Epidemiology* (10):

> "Internal Validity: The degree to which a study is free from bias or systematic error …Internal validity depends on methods used to select the study subjects, collect the relevant information, and conduct analyses ... External Validity: The degree to which results of a study may apply, be generalized to, or be transported to populations or groups that did not participate in the study." (p.287)

16. Internal validity is considered "a prerequisite for external validity" (8). Beyond their more immediate limitations, studies that lack internal validity do not have external validity and they cannot be generalized. Thus, evaluation of internal validity is a essential starting point for evaluating the adequacy of a study (or set of studies) proposed to serve as the basis for causal inference.

There is general agreement that a major issue in determining internal validity of studies, particularly observational studies, is the comparability of treatment and control groups. That view is expressed in the *Reference Manual* (9):

> "Threats to internal validity include confounding and chance differences between treatment and control groups." (p.222)

It is also found in Rothman et al. (8):

> "Internal validity implies validity of inference for the source population of study subjects … Most violations of internal validity can be classified into three general categories: confounding, selection bias, and information bias where the latter arises from mismeasurement of study variables." (p.129)

It is likewise articulated in *Dictionary of Epidemiology* (10):

> "Internal validity depends on methods used to select the study subjects, collect the relevant information, and conduct analyses. For instance, the index and comparison groups must be selected and compared in such a manner that the observed outcome differences between groups, apart from sampling error, be attributed only to the exposure of interest." (p.287)

17. Accordingly, in evaluating the evidence that sustains Dr. Samet's report, I will specifically focus on concerns of internal validity, particularly evidence of confounding.

Confounding

18. Confounding is said to occur when the association between exposure and effect is distorted by some third variable. It occurs when there is "a confusion of effects" (8):

> "On the simplest level, confounding may be considered a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of extraneous factors is mistaken for – or mixed with – the actual

> exposure effect (which may be null) ... confounding occurs only if extraneous effects become mixed with the effect under study." (8)

In general, a *confounder* is a variable that is associated with both the exposure under study and the outcome of concern. In other words, it is both an independent risk factor for that outcome and associated with the exposure under study. For example, assume an operating room offers warming devices and prophylactic antibiotics to surgical patients: some patients receive both, some receive neither, and some receive only one or the other. If the device and the antibiotics were independently associated with risk of surgical infection, then the risk of infection due to the device might be confounded by use of the antibiotic.

19. Confounding can impact any type of study, but it is of particular importance to observational studies, which by their nature are unable to fully control for many possible differences between exposed and control subjects. That concern was described in *Reference Manual* (9):

> "In a controlled experiment, the investigators decide which subjects will be exposed and which subjects will go into the control group. In observational studies, by contrast, the subjects themselves choose their exposures. Because of self-selection, the treatment and control groups are likely to differ with respect to influential factors other than the one of primary interest. (These other factors are called lurking variables or confounding variables.) … Confounding remains a problem to reckon with, even for the best observational research." (p.219)

To achieve validity in such studies, efforts should be made to minimize possible differences in the composition and treatment of the groups, other than that which is the subject of the study. For example:

> "Proper evaluation of the association between a particular exposure and a certain disease pre-supposes that every other factor which could influence disease occurrence is either constant or distributed in a balanced way between exposed and unexposed subjects." (11)

20. While it may not be possible to avoid all such problems when undertaking an observational study, it is usually possible to analyze the study, recognize the inherent problems, and then, in many cases, adjust the analysis to address the effects caused by problems such as confounding. That approach was espoused by a large group of prominent epidemiologists, including Dr. Samet, in a recently published commentary:

> "It is well known that observational epidemiologic studies may be affected by various biases that can impair their validity, and that are generally not present in experimental investigations. A strength of epidemiology is that it is based on real world conditions. Critical scrutiny of epidemiologic studies, covering all potential sources and mechanisms of biases, is indispensable." (12)

> "Epidemiologists are well aware of the potential for confounding to introduce noncausal association and generally take steps in the design and analysis phases of research to address confounding." (12)

The same thoughtful approach was advocated by Rothman and Greenland in an article that was repeatedly cited in Dr. Samet's expert report:

> "Although there are no absolute criteria for assessing the validity of scientific evidence, it is still possible to assess the validity of a study. What is required is much more than the application of a list of criteria. Instead, one must apply thorough criticism, with the goal of obtaining a quantified evaluation of the total error that afflicts the study. This type of assessment is not one that can be done easily by someone who lacks the skills and training of a scientist familiar with the subject matter and the scientific methods that were employed. Neither can it be applied readily by judges in court, nor by scientists who either lack the requisite knowledge or who do not take the time to penetrate the work." (13)

Likewise, note the following statement from the 2004 *Report on the Health Consequences of Smoking: A Report of the Surgeon General*, for which Dr. Samet was the Senior Scientific Editor:

> "If confounders are recognized and their effects measured, these effects can often be statistically minimized or removed by the analysis of a study. However, if a confounder is poorly measured, or its effects poorly characterized, then its effects cannot be controlled for in the analysis phase of a study, resulting in a causal effect that is distorted or confounded by the unwanted factor. The most extreme version of this phenomenon occurs with unmeasured confounding, causal factors that are not measured at all and whose effects are therefore not controllable, which can result in biased estimates and underestimates of uncertainty, because standard analyses implicitly assume an absence of confounding from all unmeasured factors." (14)

21. However, in his expert report, Dr. Samet was seemingly dismissive of concerns about confounding, and he apparently did not engage in a critical analysis of the potential sources of confounding and bias as he advocated in his published work. With respect to the McGovern study and suggestions that its results potentially reflected confounding, he rejected such suggestions as merely reflecting the partisan views of those who would obstruct public health initiatives:

> "This finding has been criticized as potentially reflecting confounding … These arguments are the typical general claims made by those seeking alternative explanations for an association, and reach back to the strategies employed for decades by the tobacco industry".

His analogy seems misplaced and excessive. It is all but certain that, from a public health perspective, the potential adverse effects associated with the choice of warming

devices do not rise to the level and magnitude of those associated with smoking.[2] In addition, his approach is contrary to that advocated in his writing and in the writing of others whom he apparently respects. Finally, in his actual analysis of the McGovern study, he ignored a number of potentially critical confounders. These concerns are discussed below.

The McGovern Study: Background

22. The report by McGovern et al. (15) is the only published study that purports to show an increased risk of SSI associated with the use of BH. It is the study that Dr. Samet described as the "one directly relevant observational study in the peer-reviewed literature". The published report described rates of deep-joint infection in patients who underwent "planned" primary hip and knee replacement procedures; trauma patients were excluded [Reed deposition, p. 61-62]. The procedures were performed at the Wansbeck Hospital, a component of Northumbria Healthcare Trust [Reed depo, p. 29; Albrecht depo p.144]. The report included a total of 558 hip cases and 879 knee cases performed over 27 months: 7/01/08-2/28/08, and 6/01/10-12/31/10.

23. Rates of infections documented within 60 days of surgery were reported and compared for the 20 months (7/08 thru 2/10) when the BH device was used exclusively and the 7 months (6/10 thru 12/10) when a non-FAW device was used exclusively. Results from a 3-month transition period were excluded. The data were analyzed using a univariate logistic regression that found a significantly increased odds ratio (OR) for SSI during the BH period (OR = 3.8, p=0.024). SSI were more frequent after hip than knee replacement surgeries (4.5% vs. 1.1 %).

24. The McGovern authors noted that "unfortunately" during the study period there was a change in their prophylactic antibiotic regimen and two changes in their thromboprophylaxis regimen. They did not include those two changes among the risk factors in their analyses. They also noted the "somewhat unusual" finding that risk of SSI was more than four-fold greater after hip than knee replacement, although "typically, infection risks are greater for knee replacement" (15). The increased risk after hip surgery was not affected by type of warming device.

25. The authors concluded that their study did not establish a causal basis for an association between BH and risk of SSI, largely because of various potential confounders, particularly involving infection control measures:

> "This study does not establish a causal basis for this association. Although the demographics were similar between the patient groups in terms of risk factors for infection, the data are observational and may be confounded by other infection control measures instituted by the hospital." (15)

[2] Beyond the sheer magnitude of the adverse public health effects of smoking, the association of health risks with tobacco was consistently found in dozens and dozens of studies, nearly forty at the time of the original Surgeon General's report, whereas in the present case Dr. Samet can cite only one observational study proposing a link between BH with SSI.

That concern was echoed in their deposition. For example, Mr. Albrecht:

> A. … This study simply looked at trends over time and infection rates. And the reduction in infection rates shown in the study could be due to the adoption of conductive fabric warming or it could be due to other outside factors.
> Q. What other outside factors could have influenced it?
> A. Well, it could be anything. Improvement in surgical practices, perhaps. There's an antibiotic switch that was occurring somewhere in the study's period. You could have a different group of physicians operating. These are all uncontrolled things that don't get caught with observational research.
> [Albrecht depo p. 134]

> "This is an observational study. These things aren't controlled for. You can't make a causal inference, and we did not. The study does not establish a causal basis and that's -- there's a lot of compounding factors that could be at play."[3]
> [Albrecht depo p. 178]

> "… I see other confounding factors that might be at play. I don't know. It's uncertain, like a lot of these things." [Albrecht depo p. 204]

Likewise, the deposition of Dr. McGovern:

> A. It's important to mention confounding factors, which is part of the whole purpose of not attempting to imply that this is causation … Confounding factors such as different types of thromboembolic prophylaxis, different antibiotic prophylaxis regimens, and any other measures that may be taken...
> …
> Q. And if I understood what you just said, you wanted to avoid even implying that there was a causal connection?
> A. I don't remember the precise words I used. What I mean to say is that I would not want to make a claim which was not reasonable in a paper, and based on the evidence that we had, I would not want to claim that there was a causation, or that we that proved or demonstrated a causation
> ...
> A. … we recognize there are confounding factors …there are other effects that could be at play. [McGovern depo p. 113-5]

Dr. Reed also testified as follows:

> Q.... What does it mean that there is -- that the study does not establish a causal basis?
> …

[3] I believe that this statement contains a transcription typo: the phrase "compounding factors" should have been "confounding factors", as was correctly transcribed in the following quote from that transcript.

> A. So what we have shown is association and not causation. We made that pretty clear in the paper. [Reed depo p. 229]

26. As noted, the McGovern authors were concerned about the possible effects of confounding, particularly those due to changes in antibiotic and thromboprophylaxis regimens. They also referred to "other confounding factors that might be at play", but provided no details. However, review of the published McGovern report as well as other contemporaneous and historical reports, deposition testimony, and the expert reports of Drs. Holford and Wenzel indicate a variety of confounding factors and sources of bias that potentially impacted this study in addition to the two identified in McGovern.

The McGovern Study: Sources of Confounding and Systematic Bias

27. The McGovern study focused on a time when there was a concerted effort at Wansbeck Hospital to reduce surgical infection rates because surgical infections were seemingly out-of-control. As described by Gillson and Lowdon (16), the Northumbria Healthcare Trust was regularly informed by the Health Protection Agency during 2008 and 2009 that it was "a high outlier for SSI". This was confirmed by Dr. Reed in his deposition [Reed depo p.66]. The magnitude of that excess can be appreciated by comparing the SSI rates after primary hip and knee replacement reported by McGovern to the corresponding rates for all National Health Service (NHS) hospitals in England. As reported by the NHS, between 2008 and 2011 the annual cumulative rate of SSI after primary knee replacement was less than 0.6%, and less than 0.7% after primary hip replacements (see Figures 2b and 2d in (17)). Thus, the Northumbria rates were 2- to 6-fold higher than corresponding national rates.

28. Another perspective on the SSI problem at Wansbeck Hospital is seen in an analysis of infection time trends conducted by Dr. Holford using the dataset [Albrecht depo exhibit 10] that underlies the McGovern report. As described in his report, the occurrence rates of SSI was "highly variable", with two peaks, one in late 2008 and a second more dramatic peak in late 2009-early 2010, suggesting outbreaks of infection. During the latter peak, rates were nearly 14-fold higher than the NHS average. By contrast, the lowest SSI rates were seen in late 2007 and early 2008, a time period when BH was used, but that was not included in the McGovern study.

The erratic and variable pattern of SSIs and the fact that the lowest rate of infection occurred during a nearly 9-month period when BH was used suggests that the infections reported in the McGovern study reflected infection control problems, not use of BH. The "somewhat unusual" finding that infection risks were more than four-fold greater after hip than knee replacement also suggests that infection control problems may have been unique to specific surgeons or specific surgical procedures.

29. The analysis by Dr. Holford raises another concern, the possibility that the data included in the McGovern study had been "cherry-picked". As noted above, appropriate SSI data were available for the 9 months from 10/07 to 6/08, but they were excluded from the McGovern report. Dr. Holford demonstrated that the statistically significant

difference in SSI rates between BH and non-FAW devices in the McGovern study depended on the study start date. If the McGovern authors had included one or more of the excluded months, their results would not have been significant. It is possible that exclusion of those data was unintended, but it suggests the possibility of data manipulation. And, regardless of motive, it raises important questions about the meaningfulness and generalizability of the McGovern study findings.

30. As described by Gillson and Lowdon and also by Dr. Reed in a published report (18), numerous interventions were introduced to reduce the SSI rates. Figure 2 in Gillson and Lowdon describes the "Trust Wide Surgical Site Infection Intervention Timeline for Orthopaedic THR & TKR Surgery". See also the related discussion of exhibit 5 in Dr. Reed's deposition. The list of interventions was long, but I will discuss a number of them below in more detail. This concerted effort ("The SSI Bundle") was successful: SSI rates at Northumbria Healthcare after hip and knee replacement and repair of the neck of femur declined from 5% to 0.9% (16).

31. Because so many changes were made in surgical process and procedures, it is difficult to ascribe the effort's success to any one of them individually. More notably, because SSI rates declined markedly over time, any procedure specific for the earlier time period would have appeared to be associated with higher SSI risks, while an alternative employed only during the later period would have appeared to be associated with lower risks. However, it would not be simple to conclude that such procedural changes led to the decline in rates. Given a background of steeply declining rates, it is likely that any change, even one with no actual effect, would have appeared to be beneficial. Likewise, any procedure utilized only at the beginning of the time trend would appear to have contributed to SSI. The presence of such an unequal baseline is an example of systematic bias.

The McGovern Study: Prophylactic Antibiotics

32. There were several process changes that occurred during the McGovern study time period. The authors specifically noted changes in prophylactic antibiotic regimens, but they were not included in the study analysis. Prior to 3/09, patients received a single dose of gentamicin (4.5 mg/kg). After 3/09 they received gentamicin (3 mg/kg) plus teicoplanin 400 mg. Thus, gentamicin was administered alone just during the first half of the BH time period. If use of gentamicin alone was less effective against SSI, then that could have caused BH to be associated with higher infection rates. In that case, the antibiotic regimen would be a confounder.

33. The most common bacteria causing SSI after hip and knee replacement surgery are *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, which are reported to cause 50-60% of prosthetic joint infections (19;20). An English study coauthored by Dr. Reed reported that during 2010-2013, *Staphylococcus* species represented 54.9% of SSI after hip and knee replacement (20) and a CDC study during 2006-09 found that *Staphylococcus* comprised 63% of SSI following arthroplasty (21).

34. *Staphylococcal* species have increasingly developed resistance to a spectrum of antibiotics, including gentamicin. A survey of *Staphylococcus* isolates from 19 European hospitals found that overall, 23% were gentamicin-resistant including 33% of coagulase-negative *Staphylococcus* (22). Similar data have been reported worldwide, including epidemics in individual hospitals (23;24). In discussing gentamicin resistance at the Northumbria hospitals, Dr. Reed reported that "our infection rate doubled when we went to Gentamicin" (18) and that following introduction of prophylactic gentamicin, the rate of return to theater because of SSI increased significantly, from 0.66% to 1.52% ($p<0.01$): "We recommend that single dose Gentamicin (4.5 mg/kg) alone is not used as prophylaxis for joint replacement" (25). A recent NHS report found that none of the National Trust hospitals used gentamicin alone as a prophylactic for joint replacement surgery, while 84% use teicoplanin alone or in combination with gentamicin (17).

35. Gentamicin was used alone only during the BH time period. There is evidence that *Staphylococcal* species are often resistant to gentamicin. Such resistance to gentamicin has been reported to be about 10-fold more common than resistance to teicoplanin (26). Accordingly, it is reasonable to suggest that use of gentamicin alone during the BH time period led to higher rates of SSI than were seen during the non-FAW device period, when gentamicin and teicoplanin were both used. In that case, the comparison between warming devices was confounded by the prophylactic antibiotic regimen.

The McGovern Study: MSSA Screening

36. Another procedural change during the McGovern study period was the adoption in January, 2010 of nasal screening for methicillin-sensitive *Staphylococcus aureus* (MSSA). The purpose of this intervention was to reduce the rate of SSI in the subgroup of patients who are nasal carriers of the bacteria (27;28). It is estimated that 20% (range 12-30%) of the population are persistent nasal carriers of *S aureus*, about 30% (range 16-70%) are intermittent carriers, and about 50% are non-carriers (28).

37. Nasal carriers of *Staphlococcus* have significantly higher risks of SSI than do non-carriers (29). More importantly, decolonization with a topical antibiotic, mupirocin, has been shown to significantly reduce risk of post-surgical infections including hip and knee replacement procedures (20;30;31). It is estimated that nasal screening followed by use of mupirocin reduces *Staphlococcus aureus* SSI by about 50% (30;31). In a recently published article, Dr. Reed and colleagues recommended adoption of such screening and decolonization of nasal carriers prior to joint replacement surgery (32):

> "Carriage is common (≈20%) and decolonization presents us with an easy 'high yield' strategy in the fight against PJI [prosthetic joint infection] … After MSSA screening and decolonization was introduced in one NHS joint replacement unit, the MSSA infections reduced from 0.84% to 0.26% …"

Note that his comment about the success of this approach at "one NHS joint replacement unit" specifically referenced infection rates at Northumbria Healthcare.

38. MSSA screening was performed during the last two months of the BH time period, and the entire non-FAW time period. To the extent that it reduced SSI, it would have been almost entirely during the non-FAW period. Accordingly, it is reasonable to suggest that implementation of MSSA screening would have disproportionately reduced the rate of SSI in the non-FAW cases, thereby wrongly suggesting a benefit attributable to the non-FAW device. In that case, the comparison between warming devices was confounded by the adoption of MSSA screening.

The McGovern Study: Skin Preparation

39. Another intervention that changed during the McGovern study period was the method of surgical-site skin preparation. Use of chlorhexidine-alcohol for skin preparation began in October, 2010 (16). Before that, skin preparation was performed using poviodone-iodine. Speaking of his adoption of chlorhexidine in place of poviodone, Dr. Reed opined: "If your surgeon is still using iodine plus alcohol then there is a very robust study that shows that they could do better" (18). Use of chlorhexidine - alcohol has been reported to reduce SSI by up to 40% compared to poviodone-iodine (33) and it reduced infections related to vascular catheters by 49% (34) CDC found that "high-quality evidence suggested a benefit of CHG-alcohol [chlorhexidine gluconate-alcohol] as compared with aqueous iodophor" (1). There is also evidence that the combination of MSSA screening and chlorhexidine was complementary, resulting in a five-fold reduction in deep SSI compared to the placebo (35).

40. Use of chlorhexidine for skin preparation began in October, 2010. Thus, it was used only during the last three months of the non-FAW time period. During that time, it was used in conjunction with MSSA screening. To the extent that use of chlorhexidine reduced SSI, it would have only reduced the rate of SSI in non-FAW cases, thereby wrongly suggesting a benefit attributable to the non-FAW device. In that case, the comparison between warming devices was confounded by the adoption of chlorhexidine skin preparation.

The McGovern Study: Antithrombotic Prophylaxis

41. The antithrombotic prophylaxis regimen was changed twice during the McGovern time period. Initially, patients were treated with Tinzaparin (a low molecular weight heparin). Between August, 2009 and February, 2010, that medication was replaced by Rivaroxaban (an oral anticoagulant). Then, in March 2010, Tinzaparin was reinstituted in place of Rivaroxaban. Accordingly, Rivaroxaban was administered to BH cases during those seven months; it was not administered to any non-FAW cases. According to a published report that quoted Dr. Reed, the change to Rivaroxaban was problematic: "We changed to Rivaroxaban from Tinzaparin and found that returns to theatres from wound complications more than doubled" (18). These medication changes were noted in the McGovern paper, but they were not included in the study analyses.

42. A second retrospective study was conducted at Wansbeck Hospital to evaluate the potential adverse effects of antithrombotic prophylaxis in hip and knee replacement patients. That study, the Jensen study (36), included Dr. Reed as an author. It included 489 cases treated with Rivaroxaban during six months (2/09-7/09), and 559 cases treated with Tinzaparin during seven months (8/09-2/10). The authors reported that the Rivaroxaban patients had an increased rate of deep joint infections (2.5% vs 1%), but the difference was not statistically significant. This study was cited by Dr. Samet in his report as evidence of a lack of confounding by antithrombotic medications in the McGovern study.

43. However, significant differences between the Jensen and McGovern studies invalidate that conclusion. For example, given that those two studies overlapped in time and place, and both included only patients who had undergone hip or knee replacement, one would expect that each would have reported the same number of cases for that 13-month time period. But that is not so; Jensen et al. reported significantly more cases.

44. To understand these differences, Dr. Holford reanalyzed the McGovern dataset [Albrecht depo exhibit 10] for the 13 months considered by Jensen, but applying the methodological criteria used by McGovern. For example, McGovern considered infections that developed within 60 days of surgery, while Jensen considered a 30-day window. In addition, McGovern excluded trauma patients (generally reported to have higher rates of SSI), but Jensen did not. When the McGovern approach is taken, the analysis finds that the Tinzaparin SSI rate was 0.98% and the Rivaroxaban rate was 4.5%, a statistically significant difference. In other words, analysis of the data in a manner comparable to the McGovern approach found that the antithrombotic regimen was a highly statistically significant confounder (with an odds ratio higher that that presented in the McGovern paper) that would have wrongly suggested a benefit attributable to the non-FAW device.

45. In his expert report, Dr. Samet also cited a second study, the Jameson study (37), as evidence that antithrombotic medications did not confound the infection rates reported in the McGovern study. However, the data provided in Jameson do not inform that question. Table II of that study indicates that there was no difference between the two antithrombotic medications with respect to “return to surgery for infection”, which seemingly supports Dr. Samet’s view. But, the text states that the Jameson authors, whose study pooled data from numerous hospitals, could not distinguish between cases that returned to surgery for surgical irrigation for infection and those that returned for surgical treatment of hematoma, and that the authors simply combined infections and hematomas:

> “The primary outcome measure was wound complications (including hematoma, superficial wound infection, and deep infection requiring return to surgery) within thirty days of the procedure ... It was not possible to discriminate between repeat surgical wound irrigation for infection and surgery for hematoma. However, as there is substantial overlap in the treatment and immediate health care

requirements of these conditions, it was felt that the combined data were adequate for the needs of this study." (37)

Moreover, the data provided in Table II are apparently incorrect.

45a. For the group of cases that received low molecular weight heparin (e.g., Tinzaparin), the Table indicates 291 "total wound complications", 243 of which were "managed nonoperatively" and 55 that were "return to surgery for infection". If those numbers were correct, then there would have been at least 298 complications (243 + 55 = 298), not 291. Moreover, the Table seemingly ignores cases requiring surgery because of hematoma.

45b. For the group of cases that received Rivaroxaban, the Table indicates 106 "total wound complications", 97 of which were "managed nonoperatively" and 17 that were "return to surgery for infection". If those numbers were correct, then there would have been at least 114 complications (97 + 17 = 114), not 106. And as above, the Table seemingly ignores cases requiring surgery because of hematoma.

Accordingly, it is my opinion that the Jameson report presents inconsistent data that cannot inform concerns about the potential for antithrombotic medications to confound the apparent infection rates associated with warming devices.

46. To determine the impact of the antithrombotic regimen on infection rates, Dr. Holford reanalyzed the McGovern data after controlling for its effects by comparing only BH and non-FAW device while Tinzaparin was administered. As described in his report, that analysis found no statistically significant difference between BH and non-FAW. He also performed a reanalysis that controlled for both antithrombotic and prophylactic antibiotic regimens. He compared BH and non-FAW device while both groups were medicated with Tinzaparin and Teicoplanin plus gentamicin. In that reanalysis, the infection rates in the two groups were nearly identical.

These analyses demonstrate the importance of confounding by antithrombotic regimen and prophylactic regimen.

The McGovern Study: Hawthorne Effect

47. The "Hawthorne Effect" describes a psychological phenomenon in which subjects under observation, often in a research context, modify their behavior as a consequence of being under observation. The term originated from studies conducted at Western Electric's Hawthorne plant where the effects on worker productivity of a variety of job and environmental modifications were assessed. In the original studies, productivity rose under both "positive" and "negative" conditions, which was interpreted as a result of the workers being observed and of receiving explicit feedback on their performances (38). Similar effects have been described in health care workers, who tend to comply more readily with hygiene procedures, such as use of antiseptic hand wipes, when they

are aware of being observed and when there is ongoing encouragement (39). The Hawthorne Effect is seen as a confounder of research studies because changes in performance are due to the fact that the subjects are in a study and under observation, not necessarily because of the variables that are being studied (38).

48. Consider the concerted efforts undertaken to reduce SSI at Wansbeck Hospital. The following description of that effort is from a proclamation that accompanied an award given to Northumbria Healthcare for successfully reducing its SSI rates in orthopedic surgery (40):

> "**Program Overview**: Transforming the culture and behavior of a 200-strong, multi-disciplinary team is at the heart of Northumbria's successful campaign to reduce infection rates in orthopaedic surgery.
> **The Solutions**: … The improvements in theatres included … further raising awareness among staff of the importance of infection control. Communicating the policy objectives and the progress of the improvements were key to the programme's success … updates were given regularly to a number of different groups and committees …"

Such efforts, over and beyond the choice of antibiotics, antithrombotics, skin cleansing products and warming devices, would have contributed to the reported improvements in SSI. Their impact on staff behavior would have contributed to declining rates of SSI over time, thereby wrongly suggesting a benefit attributable to the non-FAW device. In that case, the comparison between warming devices would have been confounded by something akin to the Hawthorne Effect that resulted from ongoing efforts to "transform the culture and behavior of a 200 strong multi-disciplinary team".

The McGovern Study: Data Irregularities

49. In an earlier paragraph, I noted the possibility that the McGovern study data had been "cherry picked" by selecting a starting date to ensure that the SSI rate difference between BH and non-FAW would reach statistical significance. There is also a second data irregularity, an apparent tabulation error. McGovern et al. described SSI in 32 of 1066 BH cases and 3 of 371 non-FAW cases, but there is reason to believe that one of the 32 BH infections should have been tabulated as a non-FAW infection.

50. The tabulation error can be seen by examination of the Wansbeck Hospital infection data for arthroscopic surgery, a spreadsheet that was marked as McGovern Exhibit 16. This spreadsheet, which was discussed during Dr. McGovern's second deposition, contains data on 46 surgical patients, including five treated prior to July, 2008 who were not included in the McGovern study, six treated during the three-month transition period who also were not included in the study, and 35 cases that were included in the study. The apparent error concerns patient 44, who underwent hip replacement surgery on September 15, 2010 and was then diagnosed with a *Staphylococcal* SSI on October 3, 2010. Given the dates of the patient's surgery and

diagnosis, s/he should have been included in the non-FAW group. However, column BR of the spreadsheet indicates that the patient was included instead in the BH group.

51. The fact that the data presented in the McGovern paper were not all correct was conceded by Dr. Reed in his deposition testimony:

> "It's clear to me that some of the data on the clinical side are wrong" [Reed depo p. 43].

He further testified that he had brought this to the attention of Mr. Albrecht, but it was not corrected in the final paper.

Likewise, Mr. Albrecht testified that there were conflicts between the dataset used in the published McGovern paper and an updated data file that he had also analyzed:

> "And it looks like it didn't line up a hundred percent, so I ran the analysis, I'm not sure what's going on…" [Albrecht depo p.163]

He also agreed that he had sent an email to Dr. Reed concerning those data conflicts and cautioned him not to distribute the new results:

> "I've done a quick analysis of the new data and the trend does persist, but the data files are not totally consistent (in regards to the data the brJBJS article was based upon) ... In fact, in the data file you sent me the infection rate during the forced air warming period was slightly lower than the previous one ... I'm giving you a graphic for the Wansbeck data, but do not distribute for it 'slightly' conflicts with the study data …" [Albrecht depo exhibit 12]

It seems that the McGovern authors understood that their published report contained incorrect data, but they did not correct the data and they did not subsequently publish an *erratum* or letter to the editor.

52. It is important to consider whether this tabulation error affected interpretation of the study. As described in his expert report, Dr. Holford performed such an analysis. He compared two alternatives, the data as published in McGovern (with patient case 44 in the BH group) and the corresponding data from McGovern Exhibit 16 with patient 44 included in the non-FAW group.

> **52a**. In the first analysis, infection rates were BH: 3% and non-FAW: 0.8%. The OR was 3.79, the 95% confidence interval was 1.15-12.45, and p-value using Fisher's exact test was 0.0176. Thus, the analysis demonstrated a difference that was statistically significant.

> **52b**. In the second analysis, infection rates were BH: 2.91% and non-FAW: 1.08%. The OR was 2.76, the 95% confidence interval was 0.97-10.82, and p-value using Fisher's exact test was 0.0507. Thus, in contrast to the previous

example, this analysis demonstrated a difference that was not statistically significant, as reflected by both p-value and confidence interval.

Thus that the tabulation error importantly impacted the interpretation of the study.

53. In summary, the reported conclusions of the McGovern study depend at least in part on two data irregularities. If the study had not excluded the eligible SSI data from 10/07 to 6/08, then the study would have had no significant clinical findings. Likewise, if the tabulation error described above had been corrected, then the study would have had no significant clinical findings.

The McGovern Study: Summary

54. The McGovern study, the "only directly relevant observational study" and also apparently the only study that has reported a significant SSI increase associated with BH, is fundamentally flawed. It has an inherently weak study design and it is plagued by bias, confounding, and data irregularities.

55. The study was performed during a time when infections were seemingly out-of-control. The monthly infection rates showed great variability and peaks, suggesting that whatever contributed to infection risks was inconsistent and not systematic.

56. There were numerous potential sources of confounding that were not directly considered and the authors used a univariate analysis, which failed to consider the impact of any of those factors on the infection rates attributed to the warming devices. Exhibit C, attached to this report, indicates the timelines of the McGovern study and the various Wansbeck OR procedures discussed above as potential confounders.

57. The data in the published study were incorrect, which the authors admitted but did not correct, and there is reason to suggest that the data may have been manipulated. In either event, reanalysis of the corrected data using appropriate tests indicates that the study findings were not statistically significant.

58. The authors agreed that the meaningfulness and generalizability of the study were limited because of such concerns. Thus, Mr. Albrecht testified that the study "does not establish a causal basis" [Albrecht depo p. 176] and Dr. McGovern testified: "I would not want to claim that there was a causation, or that we that proved or demonstrated a causation" [McGovern depo p. 114].

59. Accordingly, it is my opinion that the McGovern study lacks internal validity, and therefore it lacks external validity. Its results cannot be generalized.

The Samet Opinion

60. Dr. Samet concluded that "the Bair Hugger device causally increases risk for deep joint infection" based on review of the strength of association, consistency and coherence of the literature that he reviewed. I will consider those criteria separately.

61. With regard to *Strength of Association*, Dr. Samet referenced only the McGovern study, which he described as "a statistically significant association unlikely to be explained by confounding or other bias. The relative risk is estimated at 3.8". But as discussed above, the study is plagued by numerous sources of bias and confounding that were not incorporated into the analysis. Those sources of bias and confounding each tended to either increase the apparent risks of BH or decrease the apparent risks of non-FAW devices. McGovern was the only study that Dr. Samet identified that purports to show an increased risk of SSI associated with use of BH.

62. In addition, the analytical results published in McGovern and cited by Dr. Samet were based on incorrect data. When corrected, the study does not yield statistically significant results and the estimated relative risk (actually the OR) is not 3.8. Also, the first nine months of eligible data were excluded. If the data series had not been truncated, the difference in infection rates would have been even smaller (OR: 2.1, 95% confidence interval 0.75-6.0) and further from significance (p=0.2179). Thus, the apparent "strength" of this study depends on the inclusion of incorrect data and the exclusion of eligible data.

63. In discussing strength of association between BH and SSI, Dr. Samet also referred to "the studies summarized in Table 3" that considered "various tracers over the surgical site". However, none reported increased rates of SSI and therefore none contributed to the strength of association between use of BH and SSI. To the extent that they are relevant to his opinion about BH and SSI, I will consider them below in the context of *coherence*.

64. In short, it is my opinion that the McGovern study does not provide support for a finding of *strength of association b*etween BH and SSI. It is also my opinion that given the faults of the McGovern study and the apparent lack of other supporting evidence, there is no direct evidence that BH increases risks of infections in orthopedic surgical patients.

65. Dr. Samet next discussed *Consistency*, which he said "is generally applied to findings from multiple observational studies". The following is from Hill's classical description of consistency (7):

> "Consistency: Next on my list of features to be specially considered I would place the consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?"

Hill went on to exemplify consistency by reference to studies on smoking:

> "Returning to my more general example, the Advisory Committee to the Surgeon-General of the US Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries. The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that."

Because consistency "is generally applied to findings from multiple observational studies", and because the McGovern study was the "one directly relevant observational study", Dr. Samet agreed that consistency is "not applicable" to that study.

66. On the other hand, it is meaningful to consider the lack of internal consistency in the McGovern data. As discussed above and illustrated in Dr. Holford's Figure 2, the SSI rate was very inconsistent. During two time periods when BH was used, SSI rates were very low: the first nine months (that were excluded from the McGovern analysis) and the six months from 3/09 thru 8/09. At other times when BH was used, the rates were much higher, increasing nearly 16-fold at the end of 2009. Such variability suggests two discrete infection outbreaks, which were almost certainly not due to use of BH. Thus, it is clear that the data underlying McGovern are internally inconsistent.

67. The McGovern study is also inconsistent with the reported results of other studies that found no association between BH and SSI. Dr. Samet listed five such studies, which he described as "construed as 'negative' and indicating safety of forced-air warming", but which he faulted for being "seriously constrained by limited size". Without regard to the merits of those studies and their capacity to conclude a negative result, it is notable that none of them or any other of the studies cited by Dr. Samet provided evidence that BH is associated with increased rates of surgical infections. With the exception of the flawed McGovern study, there is no direct evidence that use of BH results in increased risks of infections in surgical patients.

68. Dr. Samet proposed, on the other hand, that consistency could be sought between the McGovern study and studies "on particle counts". I assume that he was referring to the first half of McGovern, an evaluation of "neutral-buoyancy detergent bubbles" which might be analogous in behavior to airborne dust particles, but not the second half of that study which reported surgical infection data. There might be consistency among the bubble/particle studies. But it is not meaningful to apply the concept of consistency as defined above to the particle studies and the clinical half of the McGovern study, because they share no "observed association" for which consistency could be sought. Particle deposition patterns are not equivalent to surgical infection rates.

69. In short, it is my opinion that the data underlying the second half of the McGovern study, the surgical infection data, were internally inconsistent. It is also my opinion that it is not meaningful to look for consistency between reports of clinical findings and the

studies “on particle counts”. However, as discussed below, the particle count studies might contribute to coherence.

70. Finally, Dr. Samet discussed *Coherence* as it applied to studies that addressed hypothetical possible mechanisms by which BH might increase the risks of joint infection. The following is from Hill’s classical description of coherence (7):

> “Coherence: On the other hand the cause-and effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease - in the expression of the Advisory Committee to the Surgeon-General it should have coherence.”

71. Dr. Samet apparently meant that those mechanistic studies were coherent with an increased risk of deep joint infections in BH users, as described in McGovern. But as already discussed, the McGovern study does not correctly demonstrate a significantly increased risk of such infections, and I am not aware of any other evidence that documents such increased risk. Therefore, there is apparently no proven disease with which the mechanistic studies can be coherent. In the absence of valid evidence of a causal association between BH and SSI, it can only be said that the mechanistic studies are coherent with a hypothetical increase in SSI. Hypothetical associations are not sufficient to sustain an inference of causation.

72. For the reasons listed above, it is my opinion that there is only insufficient evidence to support Dr. Samet’s conclusion that “the Bair Hugger device causally increases risk for deep joint infection”. A potentially causal association between BH and deep joint infections remains hypothetical and unproven.

73. Likewise, lacking sufficient and valid evidence that there is a significant causal association between BH and SSI, it is my opinion that BH does not represent a substantial contributing cause of deep joint infections.

Summary

74. Following is a list of my opinions, all to a reasonable degree of medical and scientific certainty.

> **74a**. The McGovern report is flawed by systematic bias and confounders that were ignored in the analysis. In addition, the surgical infection data presented in that report were internally inconsistent.
>
> **74b**. Accordingly, the McGovern study lacks internal validity. Because it lacks internal validity, the McGovern study also lacks external validity and cannot be generalized.

74c. The McGovern report relied on truncated and incorrectly tabulated data. When those irregularities are corrected, the study data do not provide evidence that BH is associated with a significant increase in SSI.

74d. Accordingly, the McGovern study cannot sustain Dr. Samet's opinion that "the Bair Hugger device causally increases risk for deep joint infection".

74e. There are no studies other than McGovern that show increased SSI associated with BH, and the McGovern study lacks validity and is based on incorrect data. Therefore, a causal association between BH and deep joint infections remains hypothetical and unproven.

74f. Because there is insufficient evidence that there is a significant association between BH and deep joint infections, BH does not represent a substantial contributing cause of deep joint infections.

75. I reserve the right to amend my report and opinions should further information become available.

Jonathan Borak, MD, DABT

June 02, 2017

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